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Journal

Journal of Parkinson's disease, 4(3)

ISSN

1877-7171

Authors

Krøigård, Thomas
Christensen, Jane
Wermuth, Lene
et al.

Publication Date

2014

DOI

10.3233/jpd-140386

Peer reviewed

The use of antidepressant medication in Parkinson's disease patients is not affected by the type of antiparkinson medication

Thomas Krøigård, MD[1], Jane Christensen, MSc[2], Lene Wermuth, MD[1], Beate Ritz, MD, PhD[3], and Christina F Lassen, MD, PhD[2]

[1] Department of Neurology, Odense University Hospital & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[2] Danish Cancer Society Research Centre, Danish Cancer Society, Copenhagen, Denmark

[3] Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA 90095, USA

Correspondence to:

Thomas Krøigård

Department of Neurology, Odense University Hospital, & Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark

Sdr. Boulevard 29, 5000 Odense C, Denmark.

Tel: +45 65412471; Fax: +45 65413389; Mail: tkroigaard@health.sdu.dk

Key words: Antidepressant medication, depression, dopamine agonists, levodopa, MAO-B inhibitors, Parkinson's disease.

The authors have no disclosures to report.

Sources of funding: This study was supported by a grant from the National Institutes of Environmental Health Sciences, USA (grant No R01 ES013717). Partial funding was also provided

by the National Institutes of Neurologic Diseases and Stroke, USA for the UCLA Udall Parkinson Disease Center of Excellence grant No P50 NS038367). Furthermore the study was supported financially by the Danish Parkinson's Disease Association. The funding sources had no role in the design or analysis of the study or in the decision to submit the manuscript for publication.

Abstract

Objectives: To examine whether fewer PD patients use antidepressant medication, when they are first treated with a dopamine agonist compared to other PD medications. Previous studies have suggested that dopamine agonists have an antidepressant effect in PD patients.

Methods: PD patients diagnosed in Denmark were identified using the National Hospital Register, and the diagnosis was confirmed by a review of the medical record. Antidepressant medication was assessed using the Danish National Prescription Registry. We used Cox proportional hazards regression to model the association between PD medications and time to antidepressant prescription.

Results: Of the 1,181 patients 438, 468, and 275 were first treated with levodopa, dopamine agonists and MAO-B inhibitors respectively, and 164 (37 %), 138 (29 %), and 106 (39 %) of the patients received a prescription for antidepressant medication. There was no significant difference in the hazard ratios for antidepressant prescriptions.

Conclusions: The type of PD medication first prescribed did not affect the subsequent use of antidepressants.

Introduction

Depression is one of the most important non-motor symptoms of idiopathic Parkinson's disease (PD). Depressed PD patients have reduced motor function and activities of daily living, exhibit more cognitive symptoms, and report lower quality of life than non-depressed patients. Clinical studies suggest that these consequences are reversible with adequate treatment, but depression is still underdiagnosed and undertreated in PD patients (1-3). The incidence of depression in newly diagnosed PD patients was approximately two-fold higher compared to non-PD controls in a follow-up study based on the UK-General Practice Research Database (4). A recent meta-analysis of studies assessing the prevalence of depression in PD patients reported that on average 35% of PD patients had depressive symptoms of clinical significance (5), and a diagnosis of major depression according to DSM criteria could be established in 7 to 19 %.

In contrast to depression in non-PD patients, depression in PD-patients it is most likely caused by a combination of decreased levels of dopamine and acetylcholine, as well as serotonin (6). The hypothesis that dopaminergic deficiency plays a role in depression of PD patients has stimulated some to hypothesize that treatment with dopamine agonists might be effective against depression in PD patients, in addition to alleviating motor symptoms. This notion was supported by some clinical trials (7-8), but a recent review considered the data inconclusive (1). Interestingly, the dopamine agonist pramipexole to date is the only drug considered clinically useful for treatment of depressive symptoms in PD according to the Movement Disorders Society, whereas the efficacy of the widely used selective serotonin reuptake inhibitors (SSRIs) for PD depression is still controversial (9). Specifically, a placebo-controlled trial of the SSRI citalopram in PD showed no statistically significant difference between the drug and placebo treatment (10). However, a post hoc analysis found that approximately 70% of the patients in this trial suffered from Recurrent Brief Depression in accordance with ICD-10, which is more difficult to treat than major depression.

The PASIDA study is a population-based case-control study of PD patients in Denmark treated at ten neurological departments and first identified using the National Hospital Register between 1996 and 2009, for whom the diagnosis of idiopathic PD has been confirmed by an extensive medical record review. We investigated the use of antidepressant medications in the PASIDA study population as reported in the Danish National Prescription Registry after 1995. We hypothesized that PD patients treated with a dopamine agonist first would be less likely to start using antidepressant medications compared to patients receiving treatment with levodopa or MAO-B inhibitors as dopamine agonist use would supposedly reduce the necessity for additional pharmacological treatment of depression.

Methods

From among 1,814 patients with idiopathic PD identified from the registry between 1996 and 2009 we excluded 240 patients, who already received PD medications prior to the date when the National Prescription Registry was established in 1995, 5 patients who never used PD medications according to the register, 51 patients who received their first prescription of PD medications prior to the onset of motor symptoms according to their medical record, and 337 patients who had received prescriptions of antidepressant medication prior to the prescription of PD medication. We used Cox proportional hazards regression to model associations between typical medications prescribed for Parkinson's disease symptoms and time to first SSRI or a tricyclic antidepressant prescription during the follow-up period. Age was used as the underlying time scale and follow-up was from age at first prescription of PD medications after January 1st, 1997 until prescription of an antidepressant medication, death, emigration or end of study period at December 31st, 2011, whichever came first. PD medications were defined as: Levodopa (ATC codes N04BA02 and N04BA03), agonists (ATC codes N04BC02, N04BC04 (Ropinirole), N04BC05 (Pramipexole), N04BC07, and N04BC09 (Rotigotine)) and MAO-B inhibitors (ATC codes N04BD01 and N04BD02). Antidepressants were defined by ATC codes N06AA (tricyclic antidepressants), N06AB (SSRIs), and N06AX (noradrenaline reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants).

Results

Among the 1,181 patients we followed, 438 patients were treated first with levodopa, and 468 and 275 with an agonist or a MAO-B inhibitor, respectively. 84, 73, and 69 per cent of the patients were older than 55 years at the onset of motor symptoms, and 58, 65, and 63 per cent of the patients were males in each of these treatment groups. Mean time on monotherapy was 1.8, 1.1, and 0.9 years for levodopa, agonist, and MAO-B inhibitor treated patients respectively. The mean follow-up time was 8.8, 7.1, and 9.3 years in the respective groups. No difference in the time to first prescription of an antidepressant was observed between patients who were first treated with levodopa, dopamine agonists, and MAO-B inhibitors (table 1). Separate analyses for each of the dopamine agonists pramipexole, ropinerole, and rotigotine also showed no effect on the subsequent use of antidepressants. Furthermore no differences were found in subgroups of patients defined by sex and age (data not shown).

Discussion

This study based on long-term follow-up of a relatively large number of PD patients was not able to show any difference in the use of anti-depressant medications using a Cox proportional hazards regression analysis. The most important limitation to this study is the fact that we are not able to assess the number of patients diagnosed with a clinically significant depression in our study population. The prescription patterns among the treating physicians might be influenced by other factors than depressive symptoms in the PD patients including the use of other medications such as PD medications with proposed antidepressant effects such as pramipexole or the use of MAO-B inhibitors, which are not recommended for use with SSRIs due to drug interaction problems. Furthermore, SSRIs are prescribed for other conditions than depressions including neuropathic pain, anxiety disorders, and obsessive-compulsive disorders. Another important limitation is the fact that a second PD medication was added after a relatively short duration, making it difficult to assess the effect of a single PD medication alone on the need for an anti-depressant medication.

The strength of the study is that it reflects the current clinical practice regarding the use of PD medications and treatment of depression in PD patients in a field of research where previous clinical studies have been sponsored by a drug manufacturer and have not focused specifically on depression (1). There is a need for future randomized controlled clinical trials to examine this hypothesis.

In conclusion, we were not able to confirm that treatment with a dopamine agonist delays time to antidepressant medication use compared to treatment with levodopa or MAO-B inhibitors in PD patients based on the PASIDA study population and the Danish National Prescription Registry.

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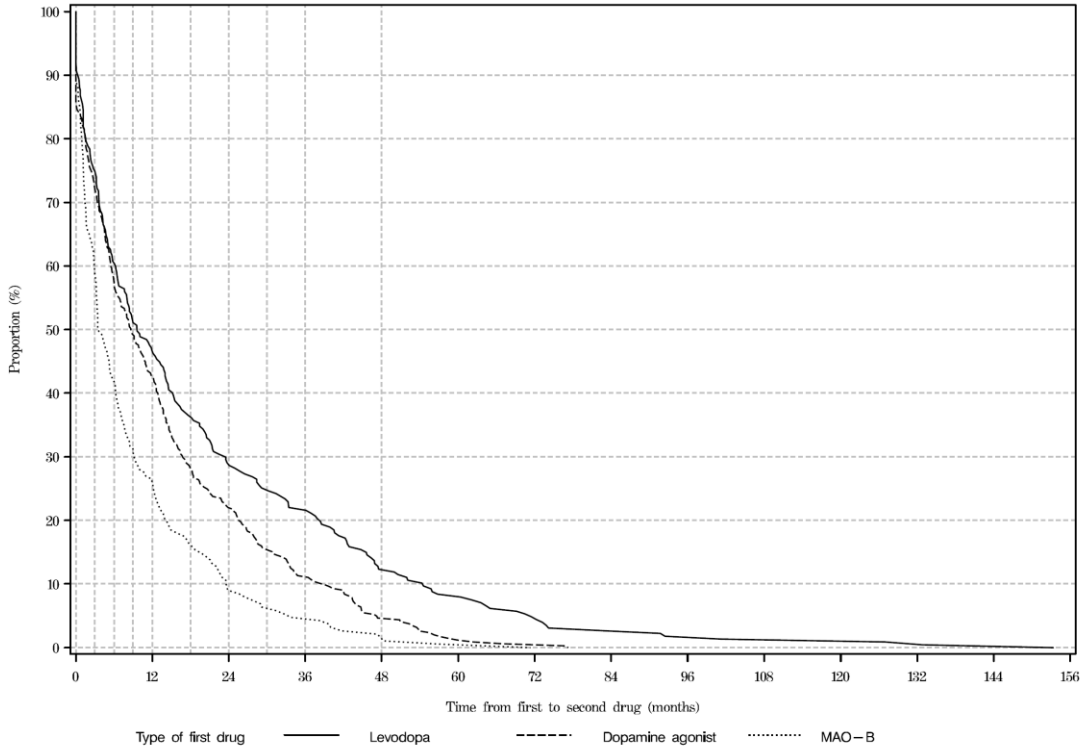

Figure S1. Time from taking the first to taking a second drug

Table 1 Demographic data, duration on PD drug monotherapy, and length of follow-up

First PD medication	**n**	**Sex (% male)**	**Age at first symptom >= 55 years (%)**	**Time on monotherapy – non-AD initiators/[BR1]AD initiators (mean in years)**	**Follow-up period – non-AD initiators/AD initiators (mean in years)**
Levodopa	438	58	84	1.7/1.9	8.8/4.3
Agonists	468	65	73	1.1/1.1	7.1/3.9
MAO-B	275	63	69	0.9/0.8	9.3/5.7
Total	1181	62	76		8.2/4.5

AD: Antidepressant medication.

Table 2 Hazard ratio (and 95% CI) for time to first anti-depressant medication prescription according to type of first PD medication prescribed

		Any antidepressant			SSRI			Tricyclic antidepressant		
	n_{total}	$n_{antidepressant}$	HR	(95% CI)	n_{SSRI}	HR	(95% CI)	n_{TCA}	HR	(95% CI)
Levodopa	438	164	1.00	-	96	1.00	-	45	1.00	-
Agonists	468	138	0.95	(0.75-1.20)	86	1.00	(0.74-1.34)	25	0.61	(0.37-1.00)
Pramipexole	234	66	0.95	(0.71-1.27)	43	1.05	(0.73-1.51)	10	0.51	(0.25-1.00)
Ropinirole	121	29	0.92	(0.82-1.38)	14	0.74	(0.42-1.30)	9	1.04	(0.51-2.15)
Rotigotine	7	2	-	-	2	-	-	0	-	-
Other types	106	41	0.95	(0.67-1.35)	27	1.06	(0.68-1.63)	6	0.49	(0.21-1.15)
MAO-B	275	106	0.97	(0.76-1.26)	60[BR2]	0.92	(0.66-1.29)	30	0.97	(0.60-1.57)

TCA: Tricyclic antidepressant

Table 3 Hazard ratio (and 95% CI) for first antidepressant medication prescription according to type of first PD medication used by sex and age

	Sex				Age at first symptom			
	Men		Women		< 55 years		≥ 55 years	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Levodopa	1.00	-	1.00	-	1.00	-	1.00	-
Agonists	0.99	(0.71-1.36)	0.94	(0.67-1.32)	0.97	(0.59-1.60)	0.93	(0.71-1.22)
MAO-B	1.09	(0.77-1.54)	0.87	(0.60-1.27)	0.83	(0.49-1.40)	1.02	(0.76-1.37)